Critical Issues in Combining Disparate Sources of Information to Estimate the Global Burden of Disease Attributable to Ambient Fine Particulate Matter Exposure

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Abstract

We develop a hybrid meta-analytic approach to estimating uncertainty from combining information on risk from a small number of studies. This method is most useful when pooling risk estimates among a limited number of studies with little observed variation compared to their sampling error. It is based on integrating features of both Frequentist and Bayesian approaches to meta-analysis. We present an example of mortality risk due to long-term exposure to ambient fine particulate matter obtained from cohort studies conducted in the United States and Europe. Study-specific pooled risk estimates are then further combined with risk information from other sources of particulate exposure at much higher concentrations, such as active and second hand smoking, to extrapolate risk from low concentrations observed in the outdoor air pollution cohort studies to the higher levels observed in developing countries. We estimate the relative risk for each study and source of particulate pollution at the range in study-specific exposure and treat these estimates as input data in order to characterize the shape of the exposure-response function. In this manner we are able to derive the form of the risk function without direct access to primary data. We thus derive a risk model that covers the entire global range in exposure. Uncertainty in risk predictions are obtained using simulation methods that incorporate uncertainty in the input source-specific risk estimates.

Key Words: ambient particulate matter, global burden of disease, uncertainty risk distribution, Bayesian analysis.

1. Introduction

There is now substantial epidemiological evidence that long-term exposure to ambient fine particulate matter ($PM_{2.5}$) contributes to the development of cardiovascular and respiratory disease, increases mortality due to these conditions and reduces life-expectancy (Brook et al., 2010). It is important for scientific and public health purposes to estimate the population health burden due to exposure to ambient concentrations of $PM_{2.5}$ in specific locations across the globe. These estimates require that the excess risk of disease or mortality be quantified in relation to long-term exposure to ambient $PM_{2.5}$ and that the uncertainty in the burden estimates from key data inputs be estimated and reported.

The most common method of estimating mortality risk from ambient $PM_{2.5}$ exposure is with a cohort study design in which a group of subjects are recruited, information on their exposure to $PM_{2.5}$ and other risk factors is obtained, and their vital status is then ascertained over time. Although the number of such studies is increasing, they are still few in number. Even when the studies are combined, the common meta-analytic methods have poor statistical properties when the number of studies examined is small. Furthermore, because the existing cohort studies have been conducted in high-income North America and Europe they provide information about risk over a relatively narrow range in ambient $PM_{2.5}$ concentrations compared to the range observed globally. Identifying the shape of a risk distribution becomes difficult under the circumstances of a narrow exposure range and relatively low predictive power. Extrapolating risks to the much higher concentrations typically observed in many regions of the world is uncertain.

In this paper we address critical issues in estimation of the shape of the exposure-response relation between ambient $PM_{2.5}$ exposure and mortality over the global range of exposure and its uncertainty. In particular, we develop a new method of combining risk estimates from a small number of studies using a hybrid Frequentist-Bayesian framework in which the prior distribution on the true risk is informed by the observed risk estimates. We also develop a new

method of extrapolating risk from the relatively low concentrations studied in US cohort studies to those concentrations observed around the world by introducing information on mortality risk from $PM_{2.5}$ exposure from disparate sources including second hand smoke, burning of biomass for heating and cooking, and active smoking.

2. Incorporating Prior Knowledge to Synthesize Information from a Small Number of Large Studies

There are many challenges in characterising uncertainty in risk. Selecting a single study, as has recently been done by the US EPA (2010) and using the sampling variations from that study likely underestimates the true uncertainty in risk.

Pooling information from different studies can be done in order to evaluate the numerical strength of evidence for an association and thus provide evidence to support a causal association if appropriate. Such pooling is also of interest when a causal association has been identified using a variety of sources of information to support the biological plausibility of the causal effect and a quantitative estimate of risk is the primary goal of the synthesis exercise. In this latter case, one could assume that the true distribution of risk among studies has only positive support and it is known or implausible that the risk factor could be negatively related to disease or mortality. Here, we suggest a Bayesian framework to facilitate pooling of information assuming that the true distribution of risk is positive although the error distribution from any single study could have substantial negative support due to large sampling uncertainty.

We consider a distribution for population health risk associated with ambient $PM_{2.5}$ based on risk estimates from a limited number of cohort studies. We propose a 2-stage Bayesian hierarchical model to estimate the distribution of risk among studies. We use a Gamma distribution for the risk to represent prior beliefs that the true but unknown risks are positive and exchangeable among the cohort studies (Brook et al., 2010).

2.1 Frequentist's Approach to Pooling

In the frequentist's approach one assumes a random effects model of the form

$$\hat{\beta}_k \sim N(\mu_\beta, \sigma_\beta^2 + \hat{v}_k^2) \quad ,$$

where $\hat{\beta}_k$ and $\hat{v}_k^2$ are the estimated study-specific risk and sampling variance of study *k*, respectively, assuming both mean risk (μ_β) and between-study heterogeneity (σ_β^2) are fixed. Estimates of $(\mu_\beta, \sigma_\beta^2)$ have been suggested using a number of approaches. A common approach used in many commercial statistical software programs uses a Q statistic (DerSimonian and Laird, 1986) based on the method of moments and large sample size. It is known that the Q statistic rejects the hull hypothesis of no heterogeneity (i.e. $\sigma_\beta^2 = 0$) too often when only a small number of studies are examined, and thus this method tends to underestimate the heterogeneity (Huedo-Medina et al., 2006). Consequently, one is led to conclude that there is stronger evidence for statistical associations between air pollution exposure and health outcome than is warranted from the observed data. Thus we are most concerned about cases in which the variation in risk estimates among studies is close to or even less than the study-specific sampling variation. In these cases the Q statistic method of estimating heterogeneity among studies often gives an estimate of zero, unrealistically suggesting no heterogeneity in the true estimate of risk. However, heterogeneity may be expected due to differences in exposure patterns, population demographics, and other unexplained risk factors.

2.2 A Hybrid Bayesian-Frequentist Approach to Pooling

In the Bayesian approach we introduce our prior beliefs and understanding into the analysis by prior distributions on $(\mu_\beta, \sigma_\beta^2)$. We first note that a set of parameters $\beta = (\beta_1, \ldots, \beta_K)$ is exchangeable if the distribution of β is unchanged if the parameters are permuted. This implies that our prior belief about β_i and β_j are the same. We can construct an exchangeable prior by assuming that the components of β are a random sample from a distribution. The parameters

β=(β_1,…, β_K) in this context represent the population risk over various cohort studies. The reported cohort risk estimates ($\hat{\beta}_k$) are then assumed to vary about the true unknown risk β_k, and the individual β_k are assumed to be random variables from a distribution conditional on additional parameters called hyperparameters. Here we assume the β_k vary over cohorts about the population mean μ_β with between-cohort variance σ_β^2.

We begin by specifying a distribution for the risk estimates ($\hat{\beta}_1$,…, $\hat{\beta}_K$), which are the estimated risk coefficients of $PM_{2.5}$ from *K* cohort studies. We assume a normal distribution for the k^{th} cohort study as follows:

$$\hat{\beta}_k \mid \beta_k \sim N(\beta_k, \hat{v}_k^2) \text{ for k} = 1,.., K,$$

where β_k is the unknown true cohort-specific risk and $\hat{v}_k^2$ is the known sampling variance of $\hat{\beta}_k$ conditional on β_k, $\hat{\text{var}}(\hat{\beta}_k \mid \beta_k)$, of the k^{th} cohort. We think that this is a reasonable assumption since the cohort studies typically have a very large number of subjects.

At the first stage of the prior, the true risks, β_1,…, β_K, are assumed to be a random sample from a distribution. Negative risks can be predicted if the uncertainty distribution has both positive and negative support, like the Normal distribution. In such cases negative risks can be truncated at zero when the distribution is used to quantify uncertainty in health benefits or the probability of the negative support is placed at zero. Selecting an uncertainty distribution with only positive support avoids these somewhat ad-hoc procedures. To illustrate our method we select a Gamma distribution with shape and scale parameters, α>0 and ϑ>0, respectively:

$$\beta_k \mid \alpha, \theta \sim G(\alpha, \theta) \text{ for any } k.$$

We select the Gamma distribution since it has only positive support which is consistent with our beliefs, based on the extensive body of literature on PM health effects (Brook et al, 2010; U.S. EPA, 2009), that exposure to ambient PM2.5 is causally linked with adverse health outcomes, and that increases in $PM_{2.5}$ cannot be plausibly associated with improved health. Other distributions with positive support could also be considered.

Since the mean risk μ_β and variance σ_β^2 of $G(\alpha,\theta)$ are $\alpha\theta$ and $\alpha\theta^2$, respectively, we can reparameterize by changing the shape and scale parameters to μ_β and σ_β^2 for convenience as follows:

$$\beta_k \mid \mu_\beta, \sigma_\beta^2 \sim G(\mu_\beta^2/\sigma_\beta^2, \sigma_\beta^2/\mu_\beta) .$$

At the second stage of the prior, the hyperparameters μ_β and σ_β^2 are assumed independent, both with Uniform distributions of the form

$$\mu_\beta \sim U(0, I_\mu) \text{ and } \sigma_\beta^2 \sim U(0, I_{\sigma^2}) .$$

For prior sensitivity, we consider a non-informative prior for μ_β and thus set I_μ to an arbitrary large number (i.e. 1000). In practice the posterior distributions for μ_β and σ_β^2 are insensitive to the prior specification of I_μ. However, they are highly sensitive to the specification of I_{σ^2}. We borrow a philosophy from the frequentist's approach by noting that the variation in risk among studies should be less than the observed variance between the $\hat{\beta}_k$. To ensure our method adheres to this philosophy we identify a value of I_{σ^2} such that the 0.975 percentile of the posterior distribution of σ_β^2 is close to but not greater than the observed variance of the $\hat{\beta}_k$. We term this method a Hybrid Bayesian-Frequentist approach.

We compare this approach assuming a Gamma distribution to a typical approach assuming a normal distribution for the true risks which is a common assumption in the Bayesian framework for meta- analysis. Here we assume

$$\beta_k \mid \mu_\beta, \sigma_\beta^2 \sim N(\mu_\beta, \sigma_\beta^2) \quad .$$

To complete the model specification we assume prior distributions for the hyperparameters

$$\mu_\beta \sim N(0, I_\mu) \text{ and } \sigma_\beta^2 \sim IG(\phi, \pi)$$

where IG is an Inverse Gamma distribution with shape and scale parameters ϕ and π for variance σ_β^2. As with the Gamma distributional assumption on the true risks, the posterior distributions for μ_β and σ_β^2 are insensitive to the specification of I_μ but highly sensitive to the

values of (ϕ,π). As with the Gamma prior specification we could select values of (ϕ,π) such that the 0.975 percentile of the estimated posterior distribution of σ_β^2 is close to but not greater than the observed variance of the $\hat{\beta}_k$. However, in most applications, the analyst selects non-informative priors such that $\mu_\beta \sim N(0,1000)$ and $\sigma_\beta^2 \sim IG(0.001,0.001)$. We take this approach here in order to compare the estimated risk distribution between the Hybrid Bayesian-Frequentist Gamma distribution and a non-informative Normal distribution.

2.3 Illustrative Example: Fine Particulate Matter association with Cause-Specific Mortality.

As part of the Global Burden of Disease 2010 project, cohort studies of ambient $PM_{2.5}$ exposure and mortality were identified for four leading causes of death: ischemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), and lung cancer (LC) (Lim et al., 2012). Eight cohort studies were included in the assessment: American Cancer Society Cancer Prevention II (ACS), Six City Study (SCS), Adventist Study of Health and Smog (ASHS), Dutch Study of Diet and Cancer (DSDC), Women's Health Initiative (WHI), Male Health Professional's Study (MHP), Nurse's Health Study (NHS), California Teachers Study (CTS). Risk estimates were not reported for all four causes of death and all eight cohorts (8 for IHD, 5 for stroke, 3 for COPD, and 4 for LC). For details on these estimates see Burnett et al. (2013).

The study and cause-of-death specific hazard ratio estimates evaluated for a difference in $PM_{2.5}$ of 10μg/m^3 are presented in Figure 1 for each cohort (horizontal dashed lines). The thickness of the lines represents the relative precision of each estimate with the ACS being by far the largest study. The estimated uncertainty distribution based on the Q statistic is represented by a blue curve. The variance of the uncertainty distribution is positive for IHD, but equals zero for stroke, COPD, and LC, thus the horizontal blue line representation implies no heterogeneity in risk among studies. The uncertainty distribution characterizes the variation in true risk and the probability distribution of a risk estimate from a newly conducted study. These results would suggest for stroke, COPD, and LC that such a new risk estimate would be for certain at the pooled estimate of the available studies, a highly unlikely scenario.

The non-informative Normal risk distribution is presented as a red curve in Figure 1. For IHD, for which the Q statistic estimated a positive heterogeneity variance, the non- informative Normal uncertainty distribution was similar to that of the Q statistic based distribution. The Gamma risk distribution based on the Hybrid Bayesian-Frequentist approach (black curve) estimated an uncertainty distribution that is skewed to the left due to the three studies with hazard ratio estimates less than or equal to one and a long tail due to the two studies with relatively large hazard ratio estimates. Here, the Gamma uncertainty distribution assigns a small probability to risk estimates similar to those from the NHS and WHI, while the Normal uncertainty distribution assign essentially no probability. The Gamma distribution also captures the evidence that some cohort studies are not detecting an association between $PM_{2.5}$ exposure and IHD mortality (MHP, ASHS, DSDC), yet not assigning a sizable proportion of uncertainty to negative risk as does the Normal distribution. By introducing a non-negative prior distribution, we can capture more of the information in the observed studies, rather than using apparent information (negative support values) that is highly implausible.

For stroke, COPD, and LC we observed a similar comparison between the uncertainty distributions based on the Q statistic, the non-informative Normal, and Gamma distribution. The Q statistic distribution is degenerate, the non-informative Normal has a very large amount of dispersion, and the Gamma distribution is more dispersed that the degenerate Q statistic uncertainty distribution but less dispersed than the non-informative Normal.

We view our Hybrid Bayesian-Frequentist approach as a reasonable compromise in cases for which the heterogeneity of risk estimate is zero based on the Q statistic, or any frequentist estimation approach, and a purely Bayesian non-formative prior approach. Assuming a zero amount of heterogeneity is unreasonable due to the large uncertainties in estimating air pollution related risk from observational epidemiological studies. Since there is a large body of non-epidemiologic evidence, as well as epidemiological evidence from other health outcomes, it is appropriate to develop informed priors, which both limit the range of the risk estimates to

the positive domain and suggest that the uncertainty in the variance of the distribution of true risks should be limited based on the observed variance in the data. Thus non-informative priors that yield much more variation in risk than that is observed among studies likely over-estimates the true uncertainty in risk.

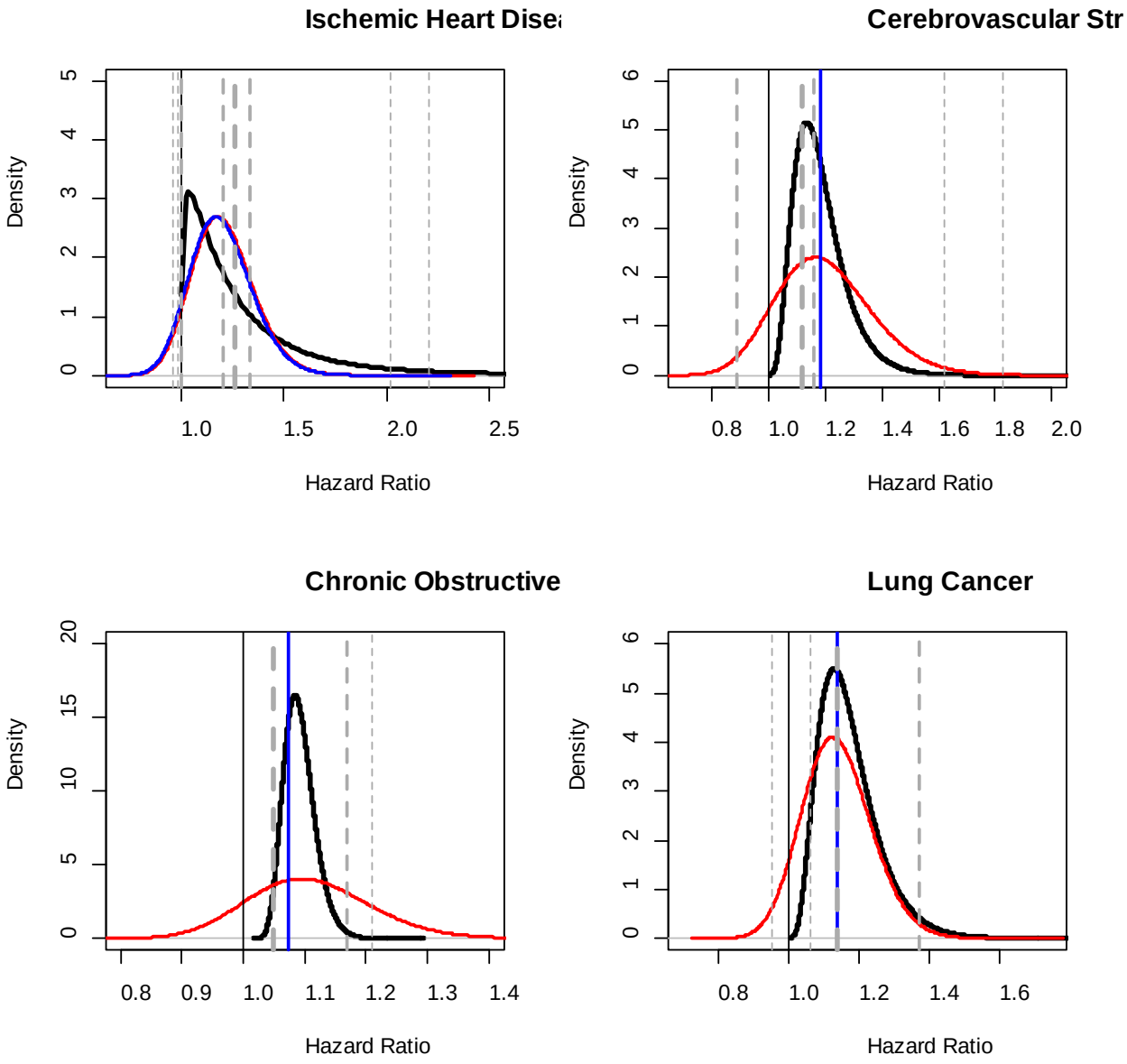

Figure 1: Gamma risk distribution with the Hybrid Bayesian-Frequentist approach (black solid line), Normal risk distribution non-informative priors (red solid line), and Normal risk distribution with Q-stat moment estimates

(blue solid line). The vertical dashed lines are reported cohort risk estimates with thickness inversely proportional to the standard error of cohort risk estimates.

3. Identifying the Shape of the $PM_{2.5}$ Mortality Exposure-Response Function

The shape and magnitude of the exposure-response relation between long-term exposure to ambient $PM_{2.5}$ and mortality has been examined using evidence obtained from cohort studies. A singular form of the concentration-response curve has not been clearly identified nor has a threshold been clearly observed. Consequently an exponential model linear in $PM_{2.5}$ has usually been preferred based on statistical inference criteria when such an examination has been conducted. However, there is evidence that for cardiovascular mortality the exposure-response function increases more rapidly at lower concentrations and the marginal increase in the excess relative risk decreases at higher exposures (Pope et al., 2009, 2011). Functional forms that have this characteristic may be better suited to predict $PM_{2.5}$ related morality risk than a linear model.

There has been little rigorous examination of the shape of the ambient $PM_{2.5}$ exposure-response function at the lowest observed levels of exposure, and it is currently unknown whether a level can be identified where there is no evidence of excess risk at the population level – a threshold level. Indirect evidence is available from studies with low mean concentrations and limited exploration of curve shapes at low levels using natural spline curve fitting. However, the specific concordance between the strength of evidence of a threshold and such assessments is not known. The limited evidence suggests that a threshold, if it exists, is well below the mean concentrations observed in the current studies. In fact, there is some evidence that the shape of the relation between cardiovascular mortality and long-term exposure to ambient $PM_{2.5}$ is supra-linear (Krewski *et al* 2009, Crouse *et al* 2012, Lepeule *et al* 2012) with the risk increasing more rapidly at lower concentrations.

Recent studies have estimated the burden of disease attributable to long-term exposure to ambient $PM_{2.5}$ in the United States (EPA 2010) and globally (Cohen et al, 2004, Anenberg et al., 2010, Evans et al., 2013). In each of these studies relative risk estimates from a single cohort study (American Cancer Society Cancer Prevention II) was used to estimate attributable burden and, in some cases, the expected benefits of reductions in exposure. The most recent studies assumed a threshold of risk or counterfactual concentration at the lowest measured concentration of $PM_{2.5}$ in the ACS study of 5.8μg/m^3. They assumed the risk function was of the form: $\exp\{\beta(PM_{2.5}-5.8)\}$ throughout the observed or modeled concentration range. They also considered a relative risk model of the logarithm of concentration of the form: $\exp\{\gamma\log(PM_{2.5})\}/\exp\{\gamma\log(5.8)\}=\left(\frac{PM_{2.5}}{5.8}\right)^{\gamma}$ which has diminishing incremental increases in relative risk as concentration increases when $\gamma<1$. Estimates of both β and γ were obtained from Krewski et al. (2009). The uncertainty in these parameter estimates was based on a single cohort study and determined by sampling uncertainty. Heterogeneity in risk among other cohort studies was not incorporated into their uncertainty characterisation.

The 95th percentile of exposure distribution of most US cohort studies is below 20 μg/m^3 and therefore reliable estimates of risk from the available studies can only be made using the data in the 5th to 95th percentile of exposure, i.e., estimates of the shape in the lower and upper 5th percentiles are both imprecise and likely to be inaccurate. Moreover, there are no cohort mortality studies that estimate the shape of the cardiovascular mortality RR function over the entire global range. Limited evidence from a large Chinese cohort (Cao et al., 2011) suggests that changes in cardiovascular mortality risk at $PM_{2.5}$ concentrations ranging from 40μg/m^3 to 160μg/m^3 are much lower than would be predicted by the US cohort study results alone (Burnett et al., 2013). This suggests that linear extrapolation of an exponential (e.g., Cox PH model) function or even using the logarithm of concentration over the entire global range of exposure would be ill-advised (Brauer et al, 2011; Burnett et al. 2013).

To illustrate the uncertainties concerning extrapolating exposure-response functions fit using a limited range in exposure to a much larger range, consider the example in Figure2.

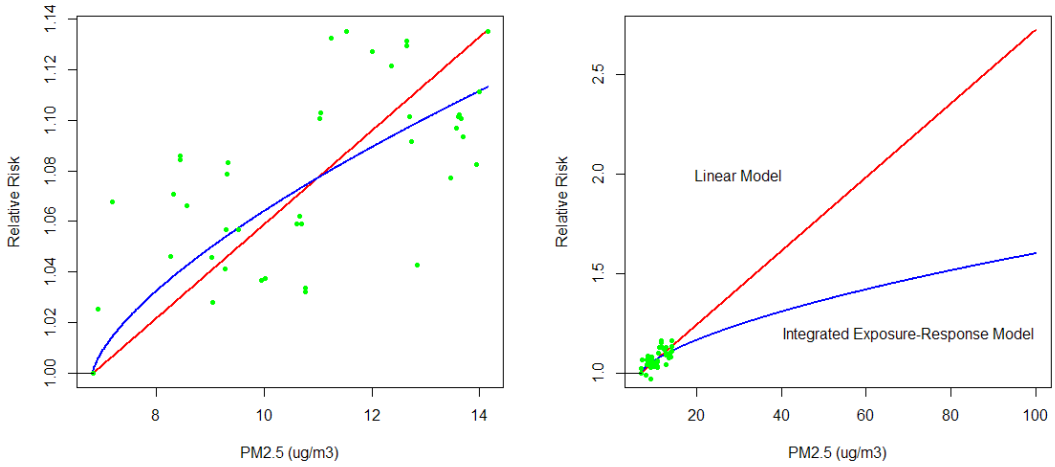

Figure 2: Linear (red solid line) and Integrated Exposuure-Response (blue solid line) fits to hypothetical data (green points) for low (left panel) and high (right panel) $PM_{2.5}$ concentrations.

The red line represents a linear model fit to the hypithetical data (green dots) while the blue line displays the fit from the supra-linear model used in the GBD 2010 project (Lim et al., 2012). Athough the two functions yield similar predictions for low $PM_{2.5}$ concentrations (left panel) they predicted very different relative risks for concentrations in the global range (right panel). Such stark differences in predcited risks suggest that methods of extrapolation based on fitting data at the low concentration range, such as was suggested by Anenberg et al. (2010) and Evans et al. (2013), are problematic.

It is a striking, but not commonly appreciated fact, that the cardiovascular mortality risk estimates from cohort studies of ambient air pollution rival in magnitude those of active cigarette smoking where exposures to combustion derived $PM_{2.5}$ are many fold higher (Pope et al 2009; 2011). For example, the hazard ratio for Ischemic Heart Disease (IHD) mortality due to ambient $PM_{2.5}$ exposure obtained from the ACS study for a change of 10µg/m^3 is 1.29 (Krewski et al, 2009). The relative risk of smoking 1-3 cigarettes per day from the same study is 1.61 (Pope et al., 2011). A change in ambient $PM_{2.5}$ concentration of 18.7µg/m^3 is associated with a

hazard ratio of 1.61. The ACS relative risk estimate is moderate compared to other cohort studies (Burnett et al., 2013).

To ensure that risk predictions over the ambient air pollution range are not implausibly larger than those observed for active smoking, Lim et al. (2012) recommend incorporating risk information from other $PM_{2.5}$ sources, including second hand and active smoking, into an integrated model. This approach provides a means to predict risk at exposure ranges for which there are direct observations without having to extrapolate risk solely based on analyses of cohort studies within a narrow exposure range as was proposed by several investigators estimating burden of disease (Anenberg et al., 2010, Evans et al, 2013). Specifically, they postulate a flexible relative risk function of the form

$$RR_{IER}(x) = \begin{cases} 1, \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots, x < x_{cf} \\ 1 + \alpha(1 - e^{-\beta(x - x_{cf})^{\rho}}), \ldots\ldots\ldots\ldots, x \geq x_{cf} \end{cases}, \quad (1)$$

where x is the concentration of $PM_{2.5}$ in $\mu g / m^3$ and x_{cf} is a counterfactual concentration below which we assume no association exists.

This Integrated Exposure-Response (IER) relative risk function is characterized by four unknown parameters $(\alpha, \beta, \rho, x_{cf})$. Here $1 + \alpha$ is the maximum risk. We include a power of $PM_{2.5}$, δ, to predict risk over a very large range of concentrations. We note that $RR_{IER}(z_{cf} + 1) \sim 1 + \alpha\beta$.

Thus, $\beta = \dfrac{RR_{IER}(z_{cf} + 1) - 1}{RR_{IER}(\infty) - 1}$ can be interpreted as the ratio of the RR at low to high exposures.

Furthermore, ρ is the relationship between $\log(PM_{2.5})$ and $\log(-\log(RR_{IER}))$.

The parameters (α, β, ρ) are estimated using curve fitting methods in which observations are drawn from relative risk estimates of outdoor air pollution studies, studies of second hand smoke, household burning of biomass for heating and cooking, and active smoking studies represented by relative risks associated with specific cigarettes/day categories.

Information on risk for specific sources is often reported based on a change in $PM_{2.5}$ exposure. For example, risk estimates from cohorts studies of ambient air pollution are reported based per μg/m^3 change. Studies of active smoking report risks between current and never cigarette smokers. Studies of $PM_{2.5}$ exposure from the burning of biomass fuels for heating and cooking construct exposure contrasts with alternate fuel sources which have non-trivial levels of $PM_{2.5}$ exposure (Smith et al., 2011). To accommodate such information we equate the observed relative risk to the ratio of the IER evaluated at the respective $PM_{2.5}$ exposures. That is

$$\hat{r}(x_U, x_L) = \frac{1+\alpha(1-\exp(-\beta(x_U - x_{cf})^{\rho})}{1+\alpha(1-\exp(-\beta(x_L - x_{cf})^{\rho})}$$

where $\hat{r}(x_U, x_L)$ is the observed relative risk associated with a contrast in $PM_{2.5}$ exposure from x_L to x_U . We set x_L and x_U to the 5th and 95th percentiles respectively of the exposure distribution of each cohort study of outdoor air pollution. We thus assume that the proportional hazards model holds over this concentration range. That is, the relative risk estimate only applies to the range in exposure observed in each study.

Lim et al. (2012) and Burnett et al. (2013) adapted a slightly different approach in which $x_L = x_{cf}$ and $x_U = \overline{x}$, the study mean concentration. In this latter approach, the study-specific relative risk estimate is applied to concentrations down to the counterfactual, which in some cases maybe much lower than the cohort study exposure range (Beelen et al., 2008; Cao et al., 2011), and up to the study mean, which is lower than the upper limits of the exposure distribution. In addition, if the counterfactual is changed the relative risk estimates used to fit the curve will also be changed since they will be evaluated at a different contrast.

Uncertainty in the relative risk function is characterized by the uncertainty in each study-specific relative risk estimate using simulation methods. Weighted non-linear curve fitting methods are used in which each relative risk estimate is weighted by the inverse of the variance of the estimate, thus giving more importance to studies with more precision. This approach also borrows strength among studies of several sources of $PM_{2.5}$ exposure in estimating uncertainty in the risk function since there are few cohort studies of ambient air pollution.

Lim et al (2012) suggest that a positive counterfactual concentration be used for burden analysis when supra-linear relative risk functions are employed. Their counterfactual concentration is bounded by the minimum concentrations observed in the studies used to estimate risk and some low percentile of the $PM_{2.5}$ distribution. There is clearly no evidence of an association below observed levels and it is impractical to estimate the shape of the curve at the extremes of the exposure distribution. Lim *et al* (2012) suggest that the 5^{th} percentile be used and that the lower and upper bounds on the counterfactual concentration be determined by the corresponding minimum and 5^{th} percentiles respectively of the American Cancer Society Cancer Prevention cohort (Krewski et al, 2009), the largest cohort study of air pollution. The minimum was 5.8 $\mu g/m^3$and the 5^{th} percentile was 8.8$\mu g/m^3$. The midpoint of this range is 7.3$\mu g/m^3$. Uncertainty in the counterfactual concentration was modelled as a uniform distribution between the minimum and 5^{th} percentile. For simplicity to illustrate our new methods we set the counterfactual concentration at 7.3$\mu g/m^3$ in all further analyses.

4. Comparison of Integrated Exposure-Response (IER) Function and Bayesian Gamma Posterior Distribution at Low Ambient $PM_{2.5}$ Concentrations

We have suggested two very different methods to synthesise information on the risk of mortality due to exposure to ambient concentrations of $PM_{2.5}$. We compare these two

approaches with respect to their estimates of risk in the ambient concentration range typically observed in North American and Europe today (i.e. $PM_{2.5}$<20μg/m^3). We also suggest methods to integrate the IER modeling approach with our new meta-analysis approach for small numbers of studies. To illustrate the comparison of approaches we consider the association between ambient $PM_{2.5}$ and mortality from Ischemic Heart Disease (IHD), the world's leading cause of death (Lim et al., 2012).

The active smoking relative risks are taken from the ACS study as reported by Pope et al. (2011). Lim et al. (2012) also used the same relative risks. However, Lim et al. (2012) included relative risks from eight studies of second hand smoke and IHD mortality reported by SGR (2006). In each study a comparison was made between low to medium SHS exposure and medium to high exposure. An equivalent $PM_{2.5}$ exposure was assigned to all eight relative risk estimates in the low-medium group of 20μg/m^3 and to the medium-high group of 50μg/m^3. All sixteen relative risks were included in the model fitting. We, however, include two relative risks based on a random effects pooling of the eight values for each group as reported by SGR (2006). For the low to medium exposure group the relative risk (95% confidence interval) was 1.16 (1.03-1.32) and for the medium to high exposure group was 1.44 (1.13-1.82) as this is the summary information taken from these studies.

For both active and SHS smoking relative risks we set x_U to the equivalent $PM_{2.5}$ concentration assigned by Pope et al. (2011) plus the counterfactual concentration and $x_L = x_{cf}$ such that the contrast in exposure employed in our model was in fact that suggested by Pope et al. (2011). The addition of the counterfactual concentration to the active smoking $PM_{2.5}$ equivalent levels makes little difference in the resulting model fits due to the very high $PM_{2.5}$ exposures assigned to active smoking, ranging from 1000 to 30000 μg/m^3. However, a counterfactual of 7.3μg/m^3 is an important contribution to the total $PM_{2.5}$ exposure for the SHS studies since their exposures are much lower than active smoking (20μg/m^3 or 50μg/m^3).

Outdoor air pollution study-specific relative risks were obtained from the Gamma model in addition to their uncertainty. These values are presented in Figure 3 for the eight cohort studies. In addition we present the observed relative risk for each study and that estimated from the non-informative Normal model. We note that the uncertainty distribution for each study-specific estimate has positive support for the Gamma model, based on the information suggesting a causal relationship between $PM_{2.5}$ and IHD mortality and the implausibility of a negative association between air pollution and IHD mortality. The estimates and uncertainty for the three methods examined are similar for the ACS study since it is by far the largest study. The three studies with non-positive observed estimates (ASHS, DSDC, MHP) are moved towards the center of the uncertainty distribution for both the Gamma and Normal models, resulting in positive central estimates while the observed relative risks for both the WHI and NHS are reduced towards to the mean. We also note that the estimate of the mean risk is larger but more uncertain for either the Normal or Gamma models compared to that derived from the Q statistic.

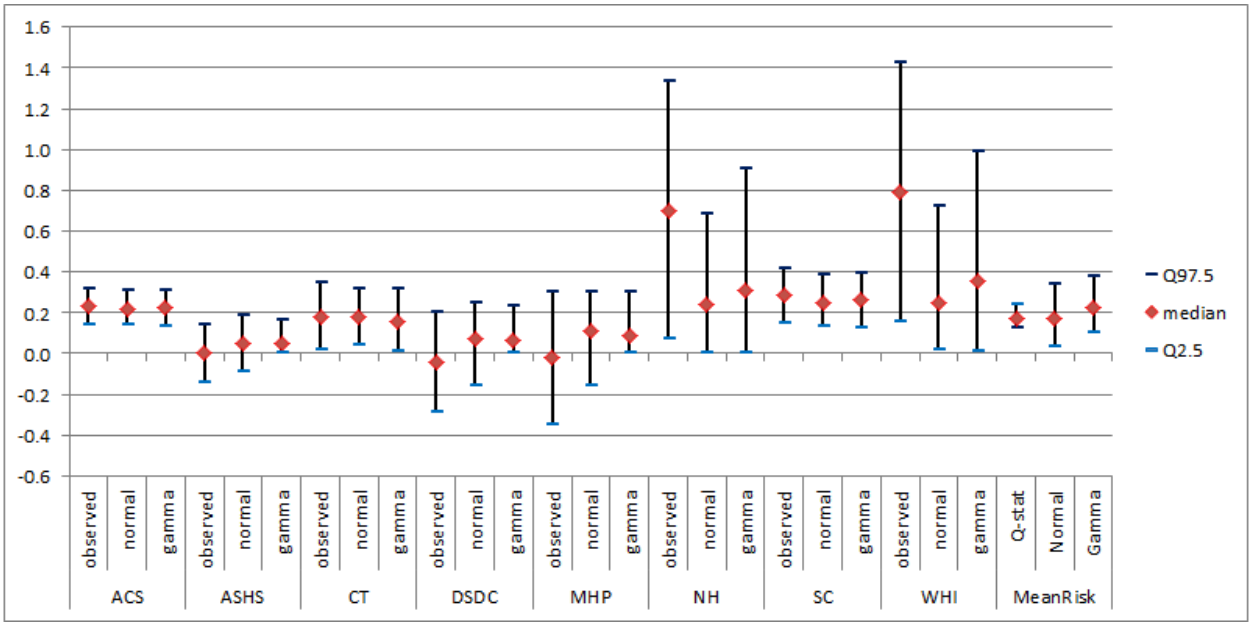

Figure 3. Median, 0.975 and 0.025 percentiles of cohort-specific uncertainty distribution for IHD mortality and mean risk by estimation method (observed, Normal model, Gamma model).

The mean values of the IER function over the simulations (solid line) and their 0.025 and 0.975 percentiles (dashed lines) are presented in Figure 4 based on our new model formulation (left hand panel) and that used by Lim et al. (2012) (right hand panel). The two curves are similar in shape and uncertainty with our new formulation yielding slightly larger values over the global $PM_{2.5}$ concentration range (<100μg/m^3) compared to that used by the GBD 2010 project and reported by Lim et al. (2012).

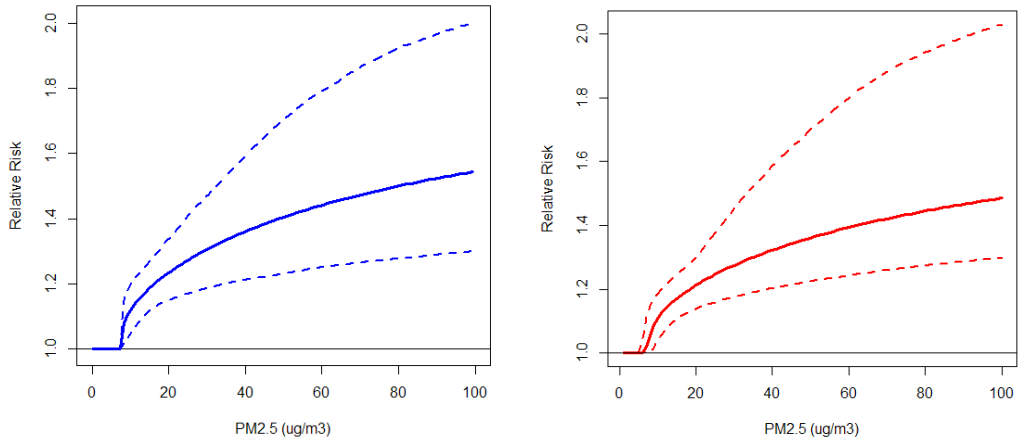

Figure 4. The mean values of the IER function over the simulations (solid line) and their 0.025 and 0.975 percentiles (dashed lines) based on current model formulation (left hand panel) and that used by GBD 2010 project (right hand panel).

We now compare the IER curve (blue line) at concentrations typically observed in North America and Europe today (<20μg/m^3) in Figure 5. In addition we present the relative risk predictions based on the mean value of the mean risk posterior distribution from the Gamma prior (exp(0.022*($PM_{2.5}$-7.3)) (red line). Although the average of these two curves is similar (1.160 for IER and 1.154 for exponential) over the 7.3 to 20μg/m^3 range, risk is distributed slightly differently by $PM_{2.5}$ concentration with larger changes in risk predicted for smaller

concentrations for the IER model compare to the exponential risk model, that is typically used in burden assessments (USEPA 2010; Anenberg et al. 2010; Evans et al. 2013).

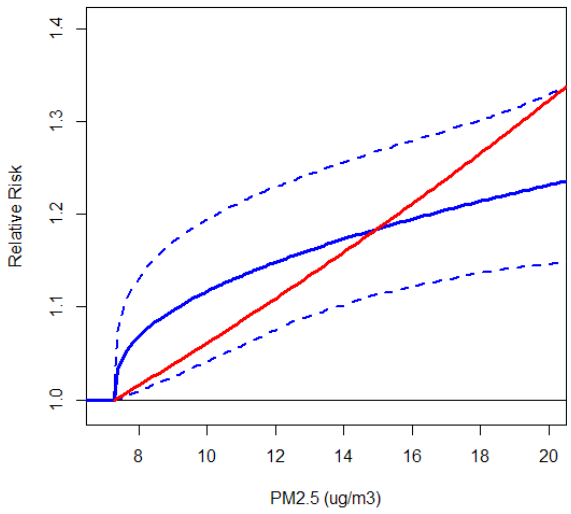

Figure 5. The mean values of the IER function over the simulations (solid blue line) and their 0.025 and 0.975 percentiles (dashed blue lines) and predicted risk based on exponential function (exp(0.022*($PM_{2.5}$-7.3)) (red line) over low $PM_{2.5}$ concentration range.

5. Discussion and Extensions

We have introduced a new method to estimate uncertainty in the true distribution of risk from a small number of studies when the variation in study-specific estimates is small compared to the within-study sampling variation. This approach borrows modeling philosophies from both the Frequentist and Bayesian approaches. We further incorporate prior knowledge, based on the large scientific literature supporting a causal relationship between $PM_{2.5}$ exposures and adverse health outcomes, to specify an uncertainty distribution that has only positive support, thus ensuring positive predictions of risk throughout the distribution. Our methods can be extended to incorporate more complex uncertainty distributions including bi-modal distributions and distributions with mass at the origin. This latter distribution is of interest when the analyst believes that there exists some non-trivial probability of a zero risk. Another extension focuses on how studies are weighted in the pooling process. Both Frequentist and Bayesian approaches all assume the observed study-specific risk is Normal with variance set to

the square of the sampling standard error. However, additional information on the quality of the study or other considerations based on expert judgment can be included in the analysis. We will report details of this approach elsewhere.

We have then shown how to incorporate information from different sources of $PM_{2.5}$ such as outdoor air, second hand and active smoking, to identify both the shape and magnitude of the relationship between exposure and response. This approach was developed originally to extrapolate risk from low concentrations used in cohort studies of air pollution from North America and Western Europe to much higher concentrations in the developing countries. This integration of information on exposure and risk was recently used by the GBD 2012 project to estimate the burden of disease from $PM_{2.5}$ worldwide (Lim et al., 2012). We have also shown that integrating information on risk from outdoor air pollution studies in the same manner as would be done in a meta-analysis specifically examining ambient air pollution risks yielded an integrated risk predictions similar to that solely based on information from outdoor air pollution cohort studies in the low concentration range for the example of ischemic heart disease mortality. Thus our IER model is generally consistent with the evidence from outdoor air pollution cohort studies in the low ambient concentration range. It is of interest to examine whether such consistency in risk predictions hold for other outcomes examined by the GBD 2012 project.

Our approach to defining the counterfactual concentration is solely based on the exposure distributions from outdoor air pollution cohort studies. There is no biological reason to believe that there exists a range in exposure for which no mortality risk exists (ie. threshold). However we have taken a conservative approach and set a positive counterfactual which may underestimate the true risk. There is some emerging evidence that the association between particulate matter exposure and mortality pertains to much lower exposures than the 5.8 to 8.8$\mu g/m^3$ range used by Lim et al. (2012). For example, the cohort study conducted in Canada (Crouse et al., 2012) showed associations in mortality risk due down to 2$\mu g/m^3$.

The Integrated-Exposure Response (IER) risk model can be used to inform risk predictions due to exposure to $PM_{2.5}$ for sources of pollution that do not have direct information on all health responses that are believed to be causally related to $PM_{2.5}$. Lim et al. (2012) report burden estimates for $PM_{2.5}$ associated with the burning of household fuel for heating and cooking for both IHD and stroke mortality for which there is no direct evidence. The IER model could be used to estimate burden due to occupational exposure since it extends to very high $PM_{2.5}$ concentrations associated with active smoking (~30,000μg/m^3) or exposure from specific sources of pollution, such as a new power plant, which for a small area surrounding the plant may yield higher exposure levels than those observed in cohort studies of ambient air.

We have selected specific studies to inform us on risk from various sources of $PM_{2.5}$ exposure. It is of interest to examine the sensitivity of the risk predictions to including other studies on these sources. We have also assigned equivalent $PM_{2.5}$ exposures based on total dose of inhaled $PM_{2.5}$ over a 24 hour period. In this manner, we are able to integrate risk information from very different sources of pollution; ambient air and active cigarette smoking for example. The sensitivity of our predictions should be examined to the assumptions made to generate these equivalent exposures.

Our approach to characterizing the shape of the exposure-response function is based on only using summary information available in the open literature: relative risk estimates and the exposure distribution for each study. We thus do not require direct access to the primary data from each study which is a major advantage since combining primary data is often not feasible due to confidentiality concerns. Our approach is only capable of distinguishing among risk functions when there is variation in exposures between studies. For example, outdoor air pollution cohort studies conducted in the United States use similar exposure data and thus have limited variation among studies. Incorporating studies of other sources of particulate pollution such as active smoking introduce considerably more variation allowing one to discriminate among functional forms.

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